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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 10/27/92 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-14 are pending in the application.
   Of the above, claims 1-8 AND 11-14 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 9-10 are rejected.
5. ☐ Claims _____ ere objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which ere acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings ere ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1 - 8, drawn to 2'-O-derivatives of purine nucleosides, classified in Class 536, subclass 27.6 and 27.81.

II. Claims 9 - 10, drawn to oligonucleotides containing at least one of the above 2'-O-modified nucleosides, classified in Class 536, subclass 24.5.

III. Claims 11 - 14, drawn to a method for using the above oligonucleotides to modulate protein synthesis, classified in Class 536, subclass 24.5 and Class 935, subclasses 33 and 44.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as two separate and distinct products. Each invention is capable of supporting a patent by itself. In addition, one would not necessarily expect a reference reading on one invention to read on the other invention as well.

Inventions I and III are related as an intermediate to a product and a method of using the product of the intermediate. Each invention is capable of supporting a patent by itself. In addition, one would not expect a reference reading on one invention to read on the other invention as well.

Inventions I and II and are related as mutually exclusive species in intermediate-final product relationship. Distinctness is proven for claims in this relationship if the intermediate product is useful to make other than the final product (M.P.E.P. 806.04(b), 3rd paragraph), and the species are patentably distinct (M.P.E.P. 806.04(h)).

In the instant case, the intermediate product is deemed to be useful as an antiviral agent and the inventions are deemed patentably distinct since there is nothing on this record to show them to be obvious variants. Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions anticipated by the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 of the other invention.

Because these inventions are distinct for the reasons given above and because they have acquired a separate status in the art as shown be their different classification and/or their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Ms. Rebecca Gaumond on June 8, 1993 a provisional election was made with traverse to prosecute the invention of Group II, claims 9 - 10. Affirmation of this election must be made by applicant in responding to this Office action. Claims 1 - 8 and 11 - 14 are withdrawn from further consideration by the Examiner, 37 C.F.R. 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. 1.48(b) and by the fee required under 37 C.F.R. 1.17(h).

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The word "novel" is superfluous and should be deleted. A suggested title is "Oligomers containing 2'-O-alkyl guanosine and 2'-O-alkyl 2-aminoadenosine".

The Abstract of the Disclosure is objected to because of the legal phraseology and because the preferred embodiments are not indicated. The applicant should indicate that the invention relates to oligonucleotides 2'-O-alkyl guanosines and 2'-O-alkyl 2-aminoadenosine and that the preferred 2'-O-alkyl groups are propyl, pentyl, nonyl, and octyl. Correction is required. See M.P.E.P. 608.01(b).

Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts, compounds or compositions, the general nature of the compound or composition should be given as well as its use, e.g., "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary. Complete revision of the content of the abstract is required on a separate sheet.

The specification is objected to because of the following informalities.

1) Throughout the disclosure the chemical structures are too faint to be interpreted unambiguously. See pages 3 - 11 and 15. Replacement pages are required.

2) On pages 7, 9, and 15, the subscript " 2 " is missing from the 2-amino group of the 2-amino-adenosine derivative.

3) On page 8, line 1, the words "having the structure" should be deleted because they are duplicates.

4) On page 13, second line from bottom: "deaminse" is a misspelling.

5) On page 24, next to last line of Example 6, the word "chromatograph" should be spelled "chromatography"

35 U.S.C. 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 9 - 10 are rejected under 35 U.S.C. 101 because the invention lacks patentable utility.

The claims are directed to oligonucleotides possessing at least one 2'-O-modified guanosine or 2'-O-modified 2-amino-adenosine nucleotide. The 2-'O-modification encompasses numerous varieties of chemical groups that have no size limits. While the R1 variable does have size limits (C3-C2-alkyl; C4-C2-alkenyl or C2-C20alkynyl), the R2 attached thereto includes "O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, Oaryl, S-aryl, NH-aryl, O-arylalkyl, S-arylalkyl, and NH-aralkyl" which **do not** have any size limits. Such large and bulky substituents, some possessing charged amino groups, will predictably created both steric and charged interactions that will interfere with and even prevent the requisite hybridization with a complementary strand. All of the above reasoning casts doubt uon the utility of the claimed oligomers as effective antisense inhibitors of nucleic express.

The specifications fail to provide even a single working example to document that one of the claimed oligonucleotides 2'-O-modified at several positions with large bulky groups such as R1 being propyl and R2 being acridine, an intercalating agent, can effectively hybridize to its complementary sequence. Without such substantiation of the utility of these oligonucleotides, the person of ordinary skill in the art would have good reason to doubt the utility of the claimed invention. This doubt is strengthen by Iribarren et al. (Proc. Natl. Acad. Sci. 87: 7747-7751, 1990) who found that oligonucleotides possessing 2'-O-dimethylallyl modifications exhibited reduced hybidiza-

tion compared to 2'-O-methyloligonucleotides. Consequently, even larger and bulkier groups as claimed by the applicant would be expected to reduce further the ability of the oligomer to hybridize effectively. Such oligonucleotides have no utility apart from their ability to hybridize to complementary sequences.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an adequate written description and failing to teach adequately how to make and/or use the invention, i.e., failing to provide an enabling disclosure.

The claims are directed to oligonucleotides possessing at least one 2'-O-modified guanosine or 2'-O-modified 2-amino-adenosine nucleotide. The 2'O-modification encompasses numerous varieties of chemical groups that have no size limits. While the R1 variable does have size limits (C3-C2-alkyl; C4-C2-alkenyl or C2-C20alkynyl), the R2 attached thereto includes "O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, Oaryl, S-aryl, NH-aryl, O-arylalkyl, S-arylalkyl, and NH-aralkyl" which **do not** have any

size limits. Such large and bulky substituents, some possessing charged amino groups, are predictably created both steric and charged interactions that will interfere with and even the requisite hybridization with a complementary strand.

The specifications fail to provide even a single working example to document that one of the claimed oligonucleotides 2'-O-modified at several nucleotides with large bulky groups such as R1 being propyl and R2 being acridine, an intercalating agent, can effectively hybridize to its complementary sequence. Without such substantiation of the utility of these oligonucleotides, the person of ordinary skill in the art would have good reason to doubt the utility of the claimed invention. This doubt is strengthen by Iribarren et al. (Proc. Natl. Acad. Sci. 87: 7747-7751, 1990) who found that oligonucleotides possessing 2'-O-dimethylallyl modifications exhibited reduced hybidization compared to 2'-O-methyloligonucleotides. Consequently, even larger and bulkier groups as claimed by the applicant would be expected to reduce further the ability of the oligomer to hybridize effectively. Such oligonucleotides have no utility apart from their ability to hybridize to complementary sequences. Inventions that are not functional certainly are not be enabled with regard to how to use.

Claims 9 - 10 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 9 - 10 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to subject matter for which there is support. See M.P.E.P. 706.03(n) and 706.03(z).

The claims read on oligonucleotides modified at the 2'-O-positions with **any intercalating agent, any reporter molecule, any conjugate, any polyamine, any polyamide, any polyalkylene glycol or any polyether.** The disclosure only adequately supports a single intercalating agent, acridine (page 18, line, second sentence in last paragraph). The term "reporter molecule" is also inadequately supported. The specification enumerates only biotin and fluorophores generally (page 18, lines 8 - 9 from bottom of page) as reporter molecules. This is not an adequate descriptive support when reporter molecules encompasses thousands of different compounds. Such radioactive molecules include C^{14}, tritium, S^{35}, or P^{32} labeled nucleotides or other organic compounds including thiophene, anthracene, or naphthalene. The claims reads on all polyamines which include such compounds as polylysine, polyarginine, polyornithine, polyspermidine, or polyspermine. However, the disclosure fails to enumerate even one specific type of polyamine. The claims read on all polyamides but the disclosure fails to enumerate any specific polyamides such as N-methyl polyamide or 2-methylpolyamide or 3-methylpolyamide. Similarly, the claims encompass all polyalkylene glycols without the disclosure

enumerating a representative number of said polyalkelene glycols. Finally, the claims encompass any "polyether", but the disclosure fails to provide a representative number of specific polyethers.

Claims 9 - 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is rendered indefinite because the subscript " 2 " is missing from the 2-amino group of the purine ring.

Claims 9 - 10 are rendered indefinite by the phrase "a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides" because this functional language does not readily permit the person of ordinary skill in the art to understand and recognize clearly the metes and bounds of the invention.

Claims 9 - 10 are rendered indefinite because of the phrase "T3 and T5 independently are OH or a further subunit of said oligomer that is joined to said structure". It is not clear that this definition rules out both T3 and T5 being hydroxyls at the same time, in which case the said oligomer becomes a single nucleoside.

Claims 9 - 10 are also rendered indefinite because the points of attachment of T3 and T5 to the oligonucleotide are not specified. T3 should connect to the 3'-terminal phosphate

of an oligonucleotides whereas T5 should connect to the 5'-terminal of an oligonucleotide.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claim 9 is rejected under 35 U.S.C. 103 as being unpatentable over Iribarren et al. (Proc. Natl. Acad. Sci. 87: 7747-7751, 1990) in view of Iribarren et al. (Proc. Nat. Acad. Sci. 87: 7747-7751, 1990).

Claim 9 is directed to an oligomer comprising at least one 2'-O-modified guanosine nucleotide. This broad generic claim reads on the 2'-O-modification being a simple haloalkyl group such as a fluoropropyl.

Cotten et al. discloses oligomers comprising at least one one guanosine ribonucleotide possessing a 2'-O-methyl or a 3'-O-ethyl group (page 2630, Figure 1). Each of these oligonucleotides were about 5-fold more effective that the natural RNA

molecule in inhibiting an mRNA processing event. The inhibition appears to be almost irreversible, presumably due to the reduced nuclease degradation and the high melting temperature of the antisense inhibitor/RNA hybrid.

The only difference between the claimed 2'-O-modified oligomers and those disclosed by Cotten et al. is the substitution of a halopropyl group for an ethyl group.

However, Iribarren et al. teaches that an allyl group is also an effective 2'-O- substituent in an oligonucleotide and actually showed less nonspecific binding without any apparent decrease in the ability to bind to target sequences (page 7750, column 2, second paragraph).

The substitution of a halogen atom such as a fluorine atom at the distal carbon of an alkyl group would not be expected to alter significantly the properties of said alkyl group because hydrogen and fluorine have the same atom diameters.

Consequently, the substitution of a 3-fluoropropyl group (which is within the genus of claim 9) for either the 2'-O-methyl of 2'-O-ethyl of Cotten et al. or the 2'-O-allyl of Iribarren et al. is well within the ability of the person of ordinary skill in the art at the time of the invention. The person of ordinary skill in the art would have, therefore, found the claimed oligomers to have been obvious over the above prior art for the purpose of creating chemically distinct

oligomers that retain the advantages of the 2'-O-alkyl modifications: **enhanced nuclease resistant and increased binding affinity to the complementary sequence.** Thus, the invention is *prima facie* obvious in the absence of clear and convincing evidence to the contrary.

Claim 10 is rejected under 35 U.S.C. 103 as being unpatentable over Cotten et al. (Nucl. Acids Res. 19: 2629 - 2635, 1991) in view of Iribarren et al. (Proc. Natl. Acad. Sci. 87: 7747-7751, 1990) and Sproat et al. (Nucl. Acids Res. 19: 733 -738, 1990).

Claim 10 is directed to oligomers comprising at least one 2-aminoadenosine nucleotides possessing a 2'-O-modified substituent.

As indicated **supra** Cotten et al. and Iribarren et al. make obvious an oligomer with at least one guanosine nucleotide possessing a 2'-O-modified alkyl group. But these two references also make obvious an oligomer with at least one adenosine nucleoside possessing a 2'-O-alkyl group (see page 2630, Fig. 1) for the same reasoning.

Sproat et al. teaches the substitution of 2-aminoadenosine for adenosine in antisense oligomers enhances the binding affinity of said oligomer to its complementary sequence (page 737, column 2, lines 4 - 10; abstract, next to last sentence; compound 5, page 736).

Consequently, an oligomer with at least one 2'-O-modified 2-aminoadenosine would also have been obvious to the person of ordinary skill in the art at the time of the invention wanting to enhance the affinity of the oligomer to its complementary sequence. Thus, the invention is prima facie obvious in the absence of clear and convincing evidence to the contrary.

Wagner et al. (Nucl. Acids. Res. 19: 5965 - 5971, 1991), Sproat et al. (Nucl. Acids Res. 18: 41 - 49, 1990), and Inoue et al. (Nucl. Acids Res. 15: 6131 - 6148, 1987) are cited from applicant's disclosure statement as addition information in the art of 2'-modified oligonucleotides.

No claim is allowed.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kunz whose telephone number is (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Gary L. Kunz 6/28/93

Gary L. Kunz:glk
June 25, 1993